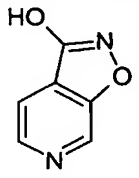
WE CLAIM:

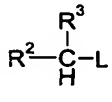
1. A method of preparing THIP comprising the steps:

a) reacting a compound of formula (2)



(2)

with an alkylating agent of formula (3)

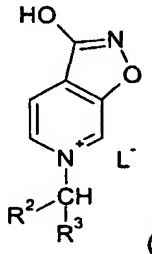


(3)

wherein R^2 and R^3 are independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, aryl, or heteroaryl, optionally substituted with a C_{1-12}alkyl, C_{1-12}alkoxy, or aryl, and

L is a leaving group,

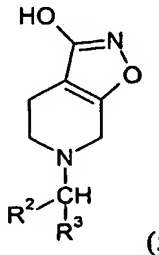
to obtain a quarternary salt of formula (4)



(4)

wherein L, R^2 and R^3 are as defined above,

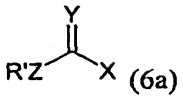
b) reacting the quarternary salt of (4) with a mild reducing agent to obtain a compound of formula (5)



(5)

wherein R^2 and R^3 are as defined above,

c) reacting a compound of formula (5) with a reagent of formula (6a)


(6a)

wherein R' is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

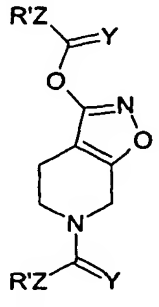
X is a leaving group,

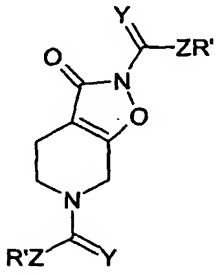
Y is O or S,

Z is O, S or C_{1-6}alkyl,

optionally followed by reaction with a nucleophile,

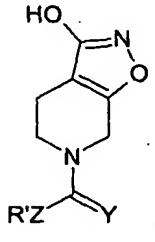
to obtain a mixture of a compound of formula (7a) and a compound of (7b)


(7a)


(7b)

wherein Y, Z, and R' are as defined above,

d) reacting the mixture of (7a) and (7b) with a nucleophile, followed by acidification, to obtain a compound of formula (8a)


(8a)

wherein Y, Z, and R' are as defined above,

e) reacting a compound of formula (8a)
with an acid to obtain THIP as an acid addition salt.

2. The method of claim 1 wherein step a) is carried out in a polar solvent, such as NMP.

3. The method of any one of claims 1-2, step a), wherein in the alkylating agent of formula (3) R^2 and R^3 are independently selected from H, methyl, ethyl, allyl, phenacyl, phenyl, methoxyphenyl and

L is selected from Br, Cl, I, OMs, or OTs.

4. The method of claim 3, wherein the alkylating agent of formula (3) is selected from MeI, EtI, BzBr, *p*-$CH_3OC_6H_4CH_2Br$, allylBr, and the corresponding mesylates (OMs) and tosylates (OTs).

5. The method of any one of claims 1-4 wherein the reduction in step b) is carried out in alcohol and water, such as aqueous ethanol.

6. The method of any one of claims 1-5 wherein the mild reducing agent in step b) is $LiBH_4$ or $NaBH_4$.

7. The method of any one of claims 1-6, step c), wherein in the reagent of formula (6a) R' is C_{1-12}alkyl, C_{1-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with a C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,
X is selected from Cl, Br, I,
Y is O, or S
Z is O, or S.

8. The method of claim 7, step c), wherein the reagent of formula (6a) is selected from C_{1-12}alkyl chloroformate, such as methyl chloroformate, ethyl chloroformate, or ethyl chlorothiolformate.

9. The method of claim 1, step c), wherein a compound of formula (5) is first protected as a carbonate or carbamate, such as a *t*-butyl- or 2,2,2-trichloroethylcarbonate/carbamate, and then reacted with the reagent of formula (6a).

10. The method of any one of claims 1-9, step d), wherein the nucleophile is a soft nucleophile, such as aqueous ammonia, an amine or diamine (such as methylamine, ethylenediamine), thiols, thiolates, sulfides, in an aqueous or organic solution.

11. The method of any one of claims 1-10, step d), wherein the reaction with a nucleophile is followed by acidification by adjusting pH to ≤ 5.

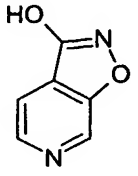
12. The method of any one of claims 1-11, wherein step d) after reaction with the nucleophile in an aqueous solution is followed by separating the aqueous phase, followed by acidification with an aqueous acid, and extraction into an organic phase.

13. The method of any one of claims 1-12, wherein a compound of formula (8a) or a salt thereof is purified by a process of extraction from one phase to another.

14. The method of any one of claims 1-13, wherein a compound of formula (8a) is obtained in high purity, more than 98%, preferably greater than 99% according to HPLC.

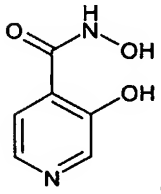
15. The method of any one of claims 1-14, wherein step e) is carried out using a mineral acid.

16. A method of preparing a compound of formula (2)



(2)

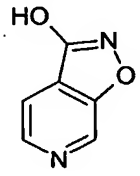
comprising reacting the compound of formula (10)



(10)

with a dehydrating agent, to obtain compound of formula (2).

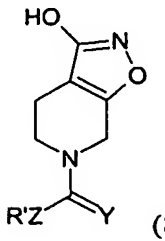
17. A compound of formula (2)



(2),

or a salt thereof.

18. A method of preparing THIP comprising reacting a compound of formula (8a) or a salt thereof



(8a)

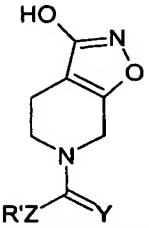
wherein R' is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

Y is O or S, and

Z is O, S or C_{1-6}alkylene,

with an acid, typically a mineral acid, to obtain THIP as an acid addition salt.

19. A compound of formula (8a)



wherein R' is C_{1-12}alkyl, C_{1-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

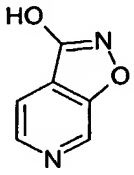
Y is O or S,

Z is O, S or C_{1-6}alkyl, or

a salt thereof.

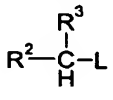
20. A method of preparing THIP comprising the steps:

a) reacting a compound of formula (2)



(2)

with an alkylating agent of formula (3)

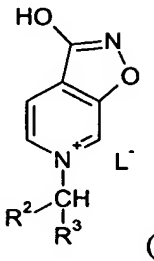


(3)

wherein R^2 and R^3 are independently selected from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, aryl, or heteroaryl, optionally substituted with a C_{1-12}alkyl, C_{1-12}alkoxy, or aryl, and

L is a leaving group,

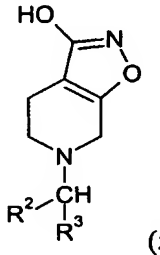
to obtain a quarternary salt of formula (4)



(4)

wherein L, R^2 and R^3 are as defined above,

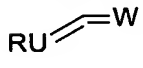
b) reacting the quarternary salt of (4) with a mild reducing agent to obtain a compound of formula (5)



(5)

wherein R^2 and R^3 are as defined above,

c2) reacting a compound of formula (5) with a reagent of formula (6b)



(6b)

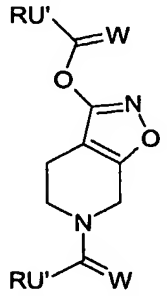
wherein R is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

U is N or CR^1, wherein R^1 is H, or R,

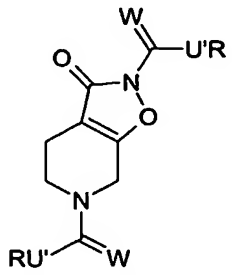
W is O, S or NR^4, wherein R^4 is H, or R,

optionally followed by reaction with a nucleophile,

to obtain a mixture of a compound of formula (7c) and a compound of (7d)



(7c)



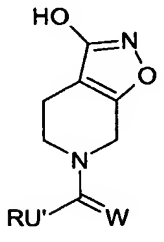
(7d)

wherein R is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

U' is N or CR^1, wherein R^1 is H, or R,

W is O, S or NR^4, wherein R^4 is H, or R,

d2) reacting the mixture of (7c) and (7d) with a nucleophile, followed by acidification, to obtain a compound of formula (8b)



(8b)

wherein W, U', and R are as defined above,

e2) reacting a compound of formula (8b) with an acid to obtain THIP as an acid addition salt.

21. The method of claim 20 wherein step a) is carried out in a polar solvent, such as NMP.

22. The method of any one of claims 20-21, step a), wherein in the alkylating agent of formula (3) R^2 and R^3 are independently selected from H, methyl, ethyl, allyl, phenacyl, phenyl, methoxyphenyl and
L is selected from Br, Cl, I, OMs, or OTs.

23. The method of claim 22, wherein the alkylating agent of formula (3) is selected from MeI, EtI, BzBr, *p*-$CH_3OC_6H_4CH_2Br$, allylBr, and the corresponding mesylates (OMs) and tosylates (OTs).

24. The method of any one of claims 20-23 wherein the reduction in step b) is carried out in alcohol and water, such as aqueous ethanol.

25. The method of any one of claims 20-24 wherein the mild reducing agent in step b) is $LiBH_4$ or $NaBH_4$.

26. The method of any one of claims 20-25, step c2), wherein in the reagent of formula (6b)
R is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or phenyl optionally substituted with a C_{1-6}alkyl, C_{1-6}alkoxy, or phenyl,
U is N or CR^1, wherein R^1 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or phenyl optionally substituted with a C_{1-6}alkyl, C_{1-6}alkoxy, or phenyl,
W is O, S or NR^4, wherein R^4 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or phenyl optionally substituted with a C_{1-6}alkyl, C_{1-6}alkoxy, or phenyl.

27. The method of any one of claims 20-26, step c2), wherein the nucleophile is selected from Cl^-, Br^-, I^-, or $NC\text{-}S^-$.

28. The method of any one of claims 26-27, step c2), wherein the reagent of formula (6b) is selected from an isocyanate such as isopropyl isocyanate or phenyl isocyanate, or an isothiocyanate such as phenyl isothiocyanate, or a ketene.

29. The method of claim 20, step c2), wherein a compound of formula (5) is first protected as a carbonate or carbamate, such as a *t*-butyl- or 2,2,2-trichloroethylcarbonate/carbamate, and then reacted with the reagent of formula (6b).

30. The method of any one of claims 20-29, step d2), wherein the nucleophile, is a soft nucleophile, such as aqueous ammonia, an amine or diamine (such as methylamine, ethylenediamine), thiols, thiolates, sulfides, in an aqueous or organic solution.

31. The method of any one of claims 20-30, step d2), wherein the reaction with a nucleophile is followed by acidification by adjusting pH to ≤ 5.

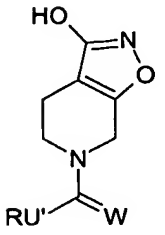
32. The method of any one of claims 20-31, wherein step d2) after reaction with the nucleophile in an aqueous solution is followed by separating the aqueous phase, followed by acidification with an aqueous acid, and extraction into an organic phase.

33. The method of any one of claims 20-32, wherein a compound of formula (8b) or a salt thereof is purified by the process of extraction from one phase to another.

34. The method of any one of claims 20-33, wherein a compound of formula (8b) is obtained in high purity, more than 98%, preferably greater than 99% according to HPLC.

35. The method of any one of claims 20-34, wherein step e2) is carried out using a mineral acid.

36. A method of preparing THIP comprising reacting a compound of formula (8b) or a salt thereof



(8b)

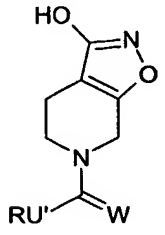
wherein, R is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

U' is NH or CHR^1, wherein R^1 is H, or R,

W is O, S or NR^4, wherein R^4 is H, or R,

with an acid, typically a mineral acid, to obtain THIP as an acid addition salt.

37. A compound of formula (8b)



(8b)

wherein, R is C_{1-12}alkyl, C_{2-12}alkenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, acyl, or aryl optionally substituted with one or more C_{1-12}alkyl, C_{1-12}alkoxy, or aryl,

U' is NH or CHR^1, wherein R^1 is H, or R,

W is O, S or NR^4, wherein R^4 is H, or R, or

a salt thereof.